

## REMARKS

After amendment, claims 94-99 remain pending in the present application, claims 1-93 having been cancelled pursuant to the filing of the instant application, the Examiner's issuance of a restriction requirement and Applicant's decision to advance prosecution of this application in seeking allowance of the presently claimed subject matter. Note that the present claims are now directed to pharmaceutical compositions. Note that the subject matter which has been cancelled from this application is cancelled *without prejudice*, in order to expedite allowance of the instant application. It is anticipated that Applicants will file one or more divisional applications directed to cancelled subject matter. No new matter has been added by way of this amendment.

The Examiner variously rejected and/or objected to previously filed claims 63-93 (claims 90-92 were indicated as being allowable ) under 35 U.S.C. §103 for the reasons which are stated in the office action on pages 2-3. Applicants respectfully submit that the claims as amended and presented do not raise issues under 35 U.S.C. §103 and should be considered allowable for the reasons which are stated hereinbelow. Applicants address each of the Examiner's rejections and consider them moot for the reasons which are set forth in the sections which follow.

### The 35 USC §103 Rejections

#### *The Rejection of Claims 63-92 over Trigo, in view of Petit and/or Saifah*

The Examiner has rejected previously pending claims 63-92 as being unpatentable over Trigo, et al., *J. Heterocyclic Chem.* (1980) 17, pp. 69-72 ("Trigo"), in view of Petit, et al., *J. Natural Products* (1984) 47, pp. 913-919 ("Petit") and/or Saifah, et al., *Natural Product* (1983) 46, pp. 352-358 ("Saifah") for the reasons which are stated in the office action on page 2. In particular, the Examiner indicates that Trigo teaches claims 5-7 on page 69, in scheme I, which correspond to claims 1, 26, 28 and 55-58 (formula A where B and C form a ring,  $n=2$  and  $R_5 = OH$ ). The Examiner cites Petit for teaching compounds 1a, 1b, 2, 3, 4a-c (page 915) as well as the composition and method of use thereof. The Examiner cites Saifah for teaching compounds 1, 2, 6a-c (page 354). The Examiner therefore concludes that previously filed claims 63-92 are

unpatentable as being obvious over a combination of the disclosure of the cited references. Applicants respectfully traverse the Examiner's rejection.

The present invention, which, in its broadest terms is claimed in claims 94-99 is directed to pharmaceutical compositions which comprise effective amounts of compounds as set forth in claims. Applicants have carefully reviewed Trigo, Petit and Saifah and submit that the presently claimed compositions are patentable over those references. Note that in the present compounds there are four substituents (two each) on the upper and lower two phenyl groups in the molecule and the hydrogen which appears between the two rings which are bridged by the nitrogen atom has a particular orientation about the carbon atom wherein the hydrogen atom is configured in an "up" or beta configuration. None of the references which are relied upon by the Examiner set forth the four substituents and the set configuration for the hydrogen as claimed in the present invention. Applicants have determined that compounds which contain a hydrogen in the configuration as claimed are far more active (anticancer) than compounds which contain a hydrogen in the same location of the molecule wherein the hydrogen is oriented in a "down" or alpha configuration. It is respectfully submitted that none of the references disclose or suggest pharmaceutical compositions as claimed.

Trigo, cited by the Examiner, describe a number of compounds, which are set forth therein, but none of the compositions are described as being particularly useful anticancer agents. Although Trigo indicates that certain compounds exhibit anti-tumor activity, those compounds are not the present invention, do not describe the present, do not have the same substituents as the compounds of the present invention and there is no disclosure or suggestion of the particular stereochemistry of the bridge hydrogen in the manner which is presently claimed. Trigo provides no structure activity relationship of the compounds which are described therein and there simply is no way of determining from Trigo what the relative contribution of each of the groups might be to pharmacological activity. In short, Trigo fails to disclose or suggest the present invention or to provide information from which one of ordinary skill could rely in order to provide pharmaceutical compositions according to the present invention.

Turning to Petit, this reference is itself deficient and does not cure any of the deficiencies of Trigo in failing to suggest or provide insight into compositions according to the present invention. Petit is directed to the isolation and structure of certain natural products. Petit does disclose certain compounds as having anti-neoplastic activity, but does not provide any structure activity relationship data associated with other compounds which are disclosed or suggested. Compounds 1a and 1b of Petit do not disclose the present invention, and do not provide information sufficiently useful to provide the present invention. Petit does not disclose the four particular substituents in the two phenyl groups of the compounds used in the present invention, and does not provide any information regarding the activity of the compounds which are disclosed therein other than compounds 1a and 1b, other than to indicate that certain compounds may be of interest for further testing. There is nothing disclosed in Petit which can be combined with Trigo to provide the present invention, because even if one of ordinary skill were to combine the teachings of Trigo with Petit, that person of ordinary skill would completely fail to understand the importance of the two substituents on each of the two phenyl groups (a teaching or suggestion which is completely absent in Trigo or Petit) or the importance of the configuration of the hydrogen on the carbon in the position alpha to R<sub>5</sub>. In short, Trigo and Petit fail to disclose or suggest the present invention.

The Examiner has also cited Saifah against the present invention in combination with Trigo and/or Petit. Saifah does nothing to obviate the failure of Trigo and Petit to disclose or suggest the present invention. Saifah simply discloses a number of constituents of the leaves of *Cissus Rheofolia*. Saifah not only does not disclose relevant pharmacological activity, it is unclear what pharmacological activity, if any, is exhibited by the Saifah disclosed compounds. Saifah provides a phytochemical investigation of the leaves of *Cissus Rheofolia* and discloses several compounds, none of which are the present compounds or suggestive of the present compounds used in the presently claimed compositions. In addition to not providing a disclosure of the full group of substituents on the phenyl rings as in the present invention, the Saifah compounds disclose an H at R<sub>5</sub>. In the only fused ring compound disclosed in Saifah (compound 1 on page 354), the stereochemistry of the bridge hydrogen (on the carbon alpha to R<sub>5</sub>), which is fixed in the present invention, is either not set or is set in a "down" or alpha configuration. In addition to Saifah not disclosing or suggesting the present pharmaceutical

compositions, Saifah does not provide any detail whatsoever about the effect of substituents on pharmacological activity, whatever that pharmacological is.<sup>1</sup> It is respectfully submitted that Saifah does not even obliquely disclose or suggest the present compositions inasmuch as the disclosed compositions are clearly distinguishable from the compounds used in the presently claimed compositions and whatever, if any, pharmacological activity is disclosed in Saifah is irrelevant to the present compositions and no structure activity relationship is disclosed.

It is respectfully submitted that the presently claimed pharmaceutical compositions are patentable over the disclosures of Trigo, in view of Petit and/or Saifah. It is respectfully submitted that that cited prior art failed to disclose or suggest the four substituents (two each) on the upper and lower phenyl groups in the basic compound or the importance of the configuration of the hydrogen on the carbon alpha to the R<sub>5</sub> substituent. Given the failure of the art to disclose or suggest the presently claimed compositions or any relevant structure activity relationship related to the present compositions, it is respectfully submitted that the presently claimed invention is patentable over the cited prior art. Applicants respectfully request the Examiner withdraw his rejection.

*The Rejection of Claim 93 over Trigo in view of Liepa*

The Examiner has rejected claim 93 over Trigo, in view of Liepa as indicated. Inasmuch as claim 93 has been cancelled, further discussion of this issue has been rendered moot. Applicants respectfully request the Examiner withdraw his rejection of claim 93.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited. Applicants have cancelled 31 claims (two independent) and added 6 claims (one independent). No fee is due for the presentation of this amendment.

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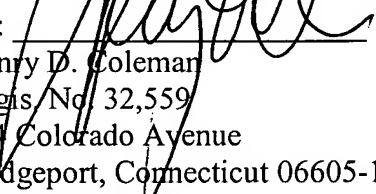
<sup>1</sup> Although Saifah does obliquely disclose biological activity, that activity is described somewhat cryptically on page 353 as activity which recovered cattle from an unspecified disease to the frustration of waiting vultures.



An extension of time of one month and the appropriate fee is submitted herewith. If any additional fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838.

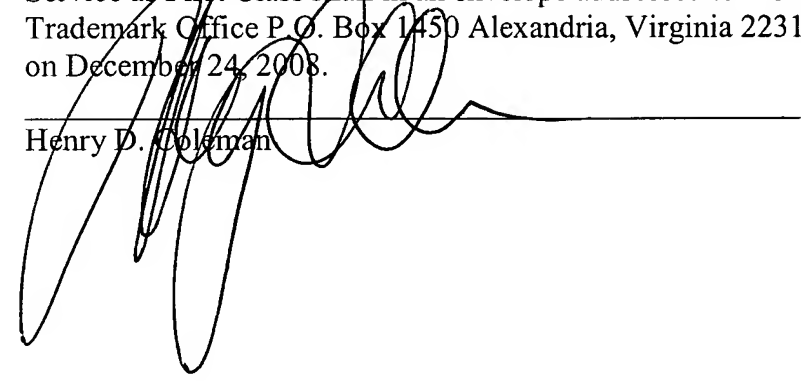
If the Examiner wishes to discuss the present application in order to advance prosecution, he is cordially requested to call the undersigned attorney at the telephone number indicated below.

Respectfully submitted,  
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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "United States Patent and Trademark Office P.O. Box 1450 Alexandria, Virginia 22313-1450" on December 24, 2008.

  
Henry D. Coleman